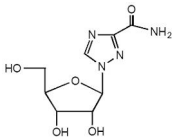
RIBAVIRIN - ribavirin capsule
Aurobindo Pharma Limited

- **RIBAVIRIN MONOTHERAPY IS NOT EFFECTIVE FOR THE TREATMENT OF CHRONIC HEPATITIS C VIRUS INFECTION AND SHOULD NOT BE USED ALONE FOR THIS INDICATION. (SEE WARNINGS).**
- **THE PRIMARY TOXICITY OF RIBAVIRIN IS HEMOLYTIC ANEMIA. THE ANEMIA ASSOCIATED WITH RIBAVIRIN THERAPY MAY RESULT IN WORSENING OF CARDIAC DISEASE THAT HAS LED TO FATAL AND NONFATAL MYOCARDIAL INFARCTIONS. PATIENTS WITH A HISTORY OF SIGNIFICANT OR UNSTABLE CARDIAC DISEASE SHOULD NOT BE TREATED WITH RIBAVIRIN. (SEE WARNINGS, ADVERSE REACTIONS, AND DOSAGE AND ADMINISTRATION).**
- **SIGNIFICANT TERATOGENIC AND/OR EMBRYOCIDAL EFFECTS HAVE BEEN DEMONSTRATED IN ALL ANIMAL SPECIES EXPOSED TO RIBAVIRIN. IN ADDITION, RIBAVIRIN HAS A MULTIPLE-DOSE HALF-LIFE OF 12 DAYS, AND SO IT MAY PERSIST IN NONPLASMA COMPARTMENTS FOR AS LONG AS 6 MONTHS. THEREFORE, RIBAVIRIN THERAPY IS CONTRAINDICATED IN WOMEN WHO ARE PREGNANT AND IN THE MALE PARTNERS OF WOMEN WHO ARE PREGNANT. EXTREME CARE MUST BE TAKEN TO AVOID PREGNANCY DURING THERAPY AND FOR 6 MONTHS AFTER COMPLETION OF TREATMENT IN BOTH FEMALE PATIENTS AND IN FEMALE PARTNERS OF MALE PATIENTS WHO ARE TAKING RIBAVIRIN THERAPY. AT LEAST TWO RELIABLE FORMS OF EFFECTIVE CONTRACEPTION MUST BE UTILIZED DURING TREATMENT AND DURING THE 6-MONTH POSTTREATMENT FOLLOW-UP PERIOD. (SEE CONTRAINDICATIONS, WARNINGS, PRECAUTIONS-INFORMATION FOR PATIENTS AND PREGNANCY CATEGORY X).**

DESCRIPTION

Ribavirin

Ribavirin is a nucleoside analog. The chemical name of ribavirin is 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and has the following structural formula:



Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The molecular formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

Ribavirin capsules consist of a white to off-white powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, povidone-K 30, and magnesium stearate. The capsule shell consists of titanium dioxide, sodium lauryl sulfate, and gelatin. The capsule is printed with edible ink containing black iron oxide.

Mechanism of Action

The mechanism of inhibition of hepatitis C virus (HCV) RNA by combination therapy with ribavirin and interferon products has not been established.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Ribavirin
Single- and multiple-dose pharmacokinetic properties in adults are summarized in **TABLE 1**. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There was a linear relationship between dose and AUC_{tf} (AUC from time zero to last measurable concentration) following single doses of 200 to 1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400 to 600 mg.

Upon multiple oral dosing, based on $AUC12_{hr}$, a sixfold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 (37%)

ng/mL. Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

Effect of Food on Absorption of Ribavirin

Both AUC_{tf} and C_{max} increased by 70% when ribavirin capsules were administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study. There are insufficient data to address the clinical relevance of these results. Clinical efficacy studies with ribavirin/INTRON A were conducted without instructions with respect to food consumption. (See **DOSAGE AND ADMINISTRATION**.)

Effect of Antacid on Absorption of Ribavirin

Coadministration of ribavirin capsules with an antacid containing magnesium, aluminum, and simethicone (Mylanta®) resulted in a 14% decrease in mean ribavirin AUC_{tf}. The clinical relevance of results from this single-dose study is unknown.

TABLE 1. Mean (% CV) Pharmacokinetic Parameters for Ribavirin Capsules When Administered Individually to Adults

Parameter	Ribavirin Capsules	
	Single Dose 600 mg Capsules (N=12)	Multiple Dose 600 mg BID Capsules (N=12)
T_{max}(hr)	1.7 (46) ***	3 (60)
C_{max}*	782 (37)	3680 (85)
AUC_{tf}**	13400 (48)	228000 (25)
$T_{1/2}$ (hr)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)	2825 (9)†	
Apparent Clearance (L/hr)	38.2 (40)	
Absolute Bioavailability	64% (44)††	

* ng/mL

** ng•hr/mL

*** N = 11

† data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N = 5

†† N = 6

Ribavirin transport into nonplasma compartments has been most extensively studied in red blood cells, and has been identified to be primarily via an e_s-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the extensive volume of distribution. Ribavirin does not bind to plasma proteins.

Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of ^{14}C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P450 enzyme-mediated metabolism of ribavirin, with minimal potential for P450 enzyme-based drug interactions.

No pharmacokinetic interactions were noted between INTRON A Injection and ribavirin capsules in a multiple-dose pharmacokinetic study.

Drug Interactions
Ribavirin has been shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine which could lead to decreased antiretroviral activity. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities (see **PRECAUTIONS: Drug Interactions**).

Special Populations

Renal Dysfunction
The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to non HCV-infected subjects with varying degrees of renal dysfunction. The mean AUC_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, AUC_{tf} was twofold greater when compared to control subjects. The increased AUC_{tf} appears to be due to reduction of renal and non-renal clearance in these patients. Phase III efficacy trials included subjects with creatinine clearance values > 50 mL/min. The multiple dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. Ribavirin is not effectively removed by hemodialysis. Patients with creatinine clearance <50 mL/min should not be treated with ribavirin (See **WARNINGS**).

Hepatic Dysfunction
The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC_{tf} values were not significantly different in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) when compared to control subjects. However, the mean C_{max} values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.

Elderly Patients
Pharmacokinetic evaluations in elderly subjects have not been performed.

Gender
There were no clinically significant pharmacokinetic differences noted in a single-dose study of eighteen male and eighteen female subjects.

INDICATIONS AND USAGE
Ribavirin capsules are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 18 years of age and older with compensated liver disease previously untreated with alpha interferon and in patients 18 years of age and older who have relapsed following alpha interferon therapy.

The safety and efficacy of ribavirin capsules with non-pegylated interferons other than INTRON A product has not been established.

Description of Clinical Studies

Ribavirin/INTRON A Combination Therapy

Adult Patients

Previously Untreated Patients
Adults with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research-based RT-PCR assay) who were previously untreated with alpha interferon therapy were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive ribavirin capsules 1200 mg/day (1000 mg/day for patients weighing ≤75 kg) plus INTRON A Injection 3 MIU TIW or INTRON A Injection plus placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The International study did not contain a 24- week INTRON A plus placebo treatment arm. The US study enrolled 912 patients who, at baseline, were 67% male, 89% Caucasian with a mean Knodell HAI score (I+II+III) of 7.5, and 72% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 799 patients (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1).

Study results are summarized in **TABLE 2**.

TABLE 2. Virologic and Histologic Responses: Previously Untreated Patients*

	US Study				International Study		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks oftreatment	
	INTRON A plus Ribavirin (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Ribavirin (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus Ribavirin (N=265)	INTRON A plus Ribavirin (N=268)	INTRON A plus Placebo (N=266)
Virologic Response[1]	65 (29)	13 (6)	85 (37)	27 (12)	86 (32)	113 (42)	46 (17)
- Responder	147 (64)	194 (84)	110 (48)	168 (75)	158 (60)	120 (45)	196 (74)
- Nonresponder	16 (7)	24 (10)	33 (14)	30 (13)	21 (8)	35 (13)	24 (9)
- Missing Data							
Histologic Response[2]	102 (45)	77 (33)	96 (42)	65 (29)	103 (39)	102 (38)	69 (26)
- Improvement	77 (34)	99 (43)	61 (27)	93 (41)	85 (32)	58 (22)	111 (41)
- No improvement	49 (21)	55 (24)	71 (31)	67 (30)	77 (29)	108 (40)	86 (32)
- Missing Data							

* Number (%) of patients.
1. Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.
2. Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of ≥2 points.

Of patients who had not achieved HCV RNA below the limit of detection of the research based assay by week 24 of ribavirin/ INTRON A treatment, less than 5% responded to an additional 24 weeks of combination treatment.

Among patients with HCV Genotype 1 treated with ribavirin/INTRON A therapy who achieved HCV RNA below the detection limit of the research-based assay by 24 weeks, those randomized to 48 weeks of treatment had higher virologic responses compared to those in the 24 week treatment group. There was no observed increase in response rates for patients with HCV nongenotype 1 randomized to ribavirin/INTRON A therapy for 48 weeks compared to 24 weeks.

Relapse Patients
Patients with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research- based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive ribavirin 1200 mg/day (1000 mg/ day for patients weighing ≤75 kg) plus INTRON A 3 MIU TIW or INTRON A plus placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The US study enrolled 153 patients who, at baseline, were 67% male, 92% Caucasian with a mean Knodell HAI score (I+II+III) of 6.8, and 58% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 192 patients (64% male, 95% Caucasian, mean Knodell score 6.6, and 56% genotype 1).

Study results are summarized in **TABLE 3.**

TABLE 3. Virologic and Histologic Responses: Relapse Patients*

	US Study		International Study	
	INTRON A plus Ribavirin N=77	**INTRON A plus Placebo N=76**	**INTRON A plus Ribavirin N=96**	**INTRON A plus Placebo N=96**
Virologic Response	33 (43)	3 (4)	46 (48)	5 (5)
- Responder[1]	36 (47)	66 (87)	45 (47)	91 (95)
- Nonresponder	8 (10)	7 (9)	5 (5)	0 (0)
- Missing Data				
Histologic Response	38 (49)	27 (36)	49 (51)	30 (31)
- Improvement[2]	23 (30)	37 (49)	29 (30)	44 (46)
- No improvement	16 (21)	12 (16)	18 (19)	22 (23)
- Missing Data				

* Number (%) of Patients.

1. Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.
2. Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of ≥2 points.

Virologic and histologic responses were similar among male and female patients in both the previously untreated and relapse studies.

CONTRAINDICATIONS

Pregnancy
Ribavirin capsules may cause birth defects and/or death of the exposed fetus. Ribavirin therapy is contraindicated for use in women who are pregnant or in men whose female partners are pregnant. (See **WARNINGS, PRECAUTIONS-Information for Patients** and **Pregnancy Category X**).

Ribavirin capsules are contraindicated in patients with a history of hypersensitivity to ribavirin or any component of the capsule.

Patients with autoimmune hepatitis must not be treated with combination ribavirin/INTRON A therapy because using these medicines can make the hepatitis worse.

Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia) should not be treated with ribavirin capsules.

WARNINGS
Based on results of clinical trials ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, ribavirin capsules must not be used alone. The safety and efficacy of ribavirin capsules with non-pegylated interferons other than INTRON A product have not been established.
There are significant adverse events caused by ribavirin/INTRON A therapy, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up. The INTRON A package insert should be reviewed in its entirety prior to initiation of combination treatment for additional safety information.

Pregnancy
RIBAVIRIN CAPSULES MAY CAUSE BIRTH DEFECTS AND/OR DEATH OF THE EXPOSED FETUS. EXTREME CARE MUST BE TAKEN TO AVOID PREGNANCY IN FEMALE PATIENTS AND IN FEMALE PARTNERS OF MALE PATIENTS. RIBAVIRIN HAS DEMONSTRATED SIGNIFICANT TERATOGENIC AND/OR EMBRYOCIDAL EFFECTS IN ALL ANIMAL SPECIES IN WHICH ADEQUATE STUDIES HAVE BEEN CONDUCTED. THESE EFFECTS OCCURRED AT DOSES AS LOW AS ONE TWENTIETH OF THE RECOMMENDED HUMAN DOSE OF RIBAVIRIN. RIBAVIRIN THERAPY SHOULD NOT BE STARTED UNTIL A REPORT OF A NEGATIVE PREGNANCY TEST

HAS BEEN OBTAINED IMMEDIATELY PRIOR TO PLANNED INITIATION OF THERAPY. PATIENTS SHOULD BE INSTRUCTED TO USE AT LEAST TWO FORMS OF EFFECTIVE CONTRACEPTION DURING TREATMENT AND DURING THE SIX MONTH PERIOD AFTER TREATMENT HAS BEEN STOPPED BASED ON MULTIPLE DOSE HALF-LIFE OF RIBAVIRIN OF 12 DAYS. PREGNANCY TESTING SHOULD OCCUR MONTHLY DURING RIBAVIRIN THERAPY AND FOR SIX MONTHS AFTER THERAPY HAS STOPPED (SEE CONTRAINDICATIONS AND PRECAUTIONS: INFORMATION FOR PATIENTS AND PREGNANCY CATEGORY X).

Anemia

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 10% of ribavirin/INTRON A-treated patients in clinical trials (See ADVERSE REACTIONS, Laboratory Values - Hemoglobin). The anemia associated with ribavirin capsules occurs within 1 to 2 weeks of initiation of therapy. BECAUSE THE INITIAL DROP IN HEMOGLOBIN MAY BE SIGNIFICANT, IT IS ADVISED THAT HEMOGLOBIN OR HEMATOCRIT BE OBTAINED PRETREATMENT AND AT WEEK 2 AND WEEK 4 OF THERAPY, OR MORE FREQUENTLY IF CLINICALLY INDICATED. Patients should then be followed as clinically appropriate.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. (See DOSAGE AND ADMINISTRATION: Guidelines for Dose Modification.) Because cardiac disease may be worsened by drug induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin. (See ADVERSE REACTIONS.)

Ribavirin and INTRON A therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

Ribavirin should not be used in patients with creatinine clearance <50 mL/min. (See **CLINICAL PHARMACOLOGY, Special Populations.**)

Pulmonary

Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis and pneumonia, have been reported during therapy with ribavirin/INTRON A; occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, the patient should be closely monitored, and if appropriate, combination ribavirin/INTRON A treatment should be discontinued.

Dental and periodontal disorders

Dental and periodontal disorders have been reported in patients receiving ribavirin and interferon combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of ribavirin and interferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition, some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

PRECAUTIONS

The safety and efficacy of ribavirin/INTRON A therapy for the treatment of HIV infection, adenovirus, RSV, parainfluenza, or influenza infections have not been established. Ribavirin capsules should not be used for these indications. Ribavirin for inhalation has a separate package insert, which should be consulted if ribavirin inhalation therapy is being considered.

The safety and efficacy of ribavirin/INTRON A therapy has not been established in liver or other organ transplant patients, patients with decompensated liver disease due to hepatitis C infection, patients who are nonresponders to interferon therapy, or patients coinfected with HBV or HIV.

Information for Patients

Patients must be informed that ribavirin capsules may cause birth defects and/or death of the exposed fetus. Ribavirin must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking ribavirin. Ribavirin should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly during therapy and for 6 months posttherapy. Women of childbearing potential must be counseled about use of effective contraception (two reliable forms) prior to initiating therapy. Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during ribavirin and for 6 months posttherapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy. (See **CONTRAINDICATIONS** and **WARNINGS**.)

If pregnancy does occur during treatment or during 6 months posttherapy, the patient must be advised of the teratogenic risk of ribavirin therapy to the fetus. Patients, or partners of patients, should immediately report any pregnancy that occurs during treatment or within 6 months after treatment cessation to their physician. Physicians should report such cases by calling 1-800-593-2214.

Patients receiving ribavirin capsules should be informed of the benefits and risks associated with treatment, directed in its appropriate use, and referred to the patient **MEDICATION GUIDE**. Patients should be informed that the effect of treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus should be taken. The complete text of the Medication Guide is reprinted at the end of this document.

The most common adverse experience occurring with ribavirin capsules is anemia, which may be severe. (See **ADVERSE REACTIONS**.) Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter. (See **Laboratory Tests**.) It is advised that patients be well hydrated, especially during the initial stages of treatment.

Laboratory Tests
The following laboratory tests are recommended for all patients treated with ribavirin capsules, prior to beginning treatment and then periodically thereafter.

- Standard hematologic tests - including hemoglobin (pretreatment, week 2 and week 4 of therapy, and as clinically appropriate [see **WARNINGS**]), complete and differential white blood cell counts, and platelet count.
- Blood chemistries - liver function tests and TSH.
- Pregnancy - including monthly monitoring for women of childbearing potential.
- ECG (See **WARNINGS**)

Carcinogenesis and Mutagenesis
Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was noncarcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult). However, this dose was less than the maximum tolerated dose, and therefore the study was not adequate to fully characterize the carcinogenic potential of ribavirin.

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20 to 200 mg/kg (estimated human equivalent of 1.67 to 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 to 1 X the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.
Impairment of Fertility

Ribavirin demonstrated significant embryocidal and/or teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted.

Fertile women and partners of fertile women should not receive ribavirin unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilized for 6 months posttherapy (e.g., 15 half-lives of clearance for ribavirin).

Ribavirin should be used with caution in fertile men. In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 to 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 to 0.8 X the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

Animal Toxicology

Long-term studies in the mouse and rat (18 to 24 months; doses of 20 to 75 and 10 to 40 mg/kg/day, respectively {estimated human equivalent doses of 1.67 to 6.25 and 1.43 to 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 to 0.4 X the maximum human 24-hour dose of ribavirin}) have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

In a study in which rat pups were dosed postnatally with ribavirin at doses of 10, 25 and 50 mg/kg/day, drug-related deaths occurred at 50 mg/kg (at rat pup plasma concentrations below human plasma concentrations at the human therapeutic dose) between study days 13 and 48). Rat pups dosed from postnatal day 7 through 63 demonstrated a minor, dose-related decrease in overall growth at all doses, which was subsequently manifested as slight decreases in body weight, crown-rump length and bone length. These effects showed evidence of reversibility, and no histopathological effects on bone were observed. No ribavirin effects were observed regarding neurobehavioral or reproductive development.

Pregnancy
Pregnancy Category X: (see CONTRAINDICATIONS) – Ribavirin Pregnancy Registry

Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 X the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 X the maximum recommended human 24-hour dose of ribavirin).
Treatment and Posttreatment
Potential Risk to the Fetus

Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 to 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 X the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

Women of childbearing potential should not receive ribavirin unless they are using effective contraception (two reliable forms) during the therapy period. In addition, effective contraception should be utilized for 6 months posttherapy based on a multiple-dose half-life ($t_{1/2}$) of ribavirin of 12 days.

Male patients and their female partners must practice effective contraception (two reliable forms) during treatment with ribavirin and for the 6-month posttherapy period (e.g., 15 half-lives for ribavirin clearance from the body).
Ribavirin Pregnancy Registry
A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for six months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

Nursing Mothers
It is not known whether the ribavirin product is excreted in human milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to delay or discontinue ribavirin.

Geriatric Use
Clinical studies of ribavirin/INTRON A therapy did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently from younger subjects.

Ribavirin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments should be made accordingly. Ribavirin should not be used in patients with creatinine clearance <50 mL/min. (See **WARNINGS**.)

In general, ribavirin capsules should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic and/or cardiac function, and of concomitant disease or other drug therapy. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than did younger patients (28%). (See **WARNINGS**.)

Pediatric Use
Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up (see WARNINGS). As in adult patients, pediatric

patients experienced other psychiatric adverse events (e.g., depression, emotional lability, somnolence), anemia, and neutropenia (see **WARNINGS**). During a 48-week course of therapy there was a decrease in the rate of linear growth (mean percentile assignment decrease of 9%) and a decrease in the rate of weight gain (mean percentile assignment decrease of 13%). A general reversal of these trends was noted during the 24--week post-treatment period.

Drug Interactions

Didanosine

Co-administration of ribavirin capsules and didanosine is not recommended. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactactemia/lactic acidosis have been reported in clinical trials (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

Stavudine and Zidovudine

Ribavirin may antagonize the *in vitro* antiviral activity of stavudine and zidovudine against HIV. Therefore, concomitant use of ribavirin with either of these drugs should be used with caution (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

ADVERSE REACTIONS

The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1 to 2 weeks of oral therapy. (See WARNINGS.) Cardiac and pulmonary events associated with anemia occurred in approximately 10% of patients. (See WARNINGS.)

Ribavirin/INTRON A Combination Therapy

In clinical trials, 19% and 6% of previously untreated and relapse patients, respectively, discontinued therapy due to adverse events in the combination arms compared to 13% and 3% in the interferon arms. Selected treatment-emergent adverse events that occurred in the US studies with ≥5% incidence are provided in **TABLE 4** by treatment group. In general, the selected treatment-emergent adverse events were reported with lower incidence in the international studies as compared to the US studies with the exception of asthenia, influenza-like symptoms, nervousness, and pruritus.

TABLE 4. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Adult Patients

Percentage of Patients

	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
Patients Reporting Adverse Events*	INTRON A plus Ribavirin (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Ribavirin (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus Ribavirin (N=77)	INTRON A plus Placebo (N=76)
Application Site Disorders						
Injection Site	13	10	12	14	6	8
Inflammation	7	9	8	9	5	3
Injection Site Reaction						
Body as a Whole - General Disorders	63	63	66	67	66	68
	68	62	70	72	60	53
Headache	40	32	42	39	43	37
Fatigue	37	35	41	40	32	36
Rigors	14	18	18	20	13	13
Fever	9	4	9	9	10	4
Influenza-like symptoms	5	4	9	8	6	7
Asthenia						
Chest pain						
Central &						

Peripheral Nervous System Disorders	17	15	23	19	26	21
Dizziness						
Gastrointestinal System Disorders						
Nausea	38	35	46	33	47	33
Anorexia	27	16	25	19	21	14
Dyspepsia	14	6	16	9	16	9
Vomiting	11	10	9	13	12	8
Musculoskeletal System Disorders						
Myalgia	61	57	64	63	61	58
Arthralgia	30	27	33	36	29	29
Musculoskeletal pain	20	26	28	32	22	28
Psychiatric Disorders	39	27	39	30	26	25
Insomnia	23	19	32	27	25	20
Irritability	32	25	36	37	23	14
Depression	7	6	11	8	12	8
Emotional lability	11	14	14	14	10	12
Concentration impaired	4	2	4	4	5	4
Nervousness						
Respiratory System Disorders	19	9	18	10	17	12
Dyspnea	9	7	10	14	12	7
Sinusitis						
Skin and Appendages Disorders	28	27	32	28	27	26
Alopecia	20	9	28	8	21	5
Rash	21	9	19	8	13	4
Pruritus						
Special Senses, Other Disorders	7	4	8	4	6	5
Taste perversion						

* Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/organ class category.

In addition, the following spontaneous adverse events have been reported during the marketing surveillance of ribavirin/INTRON A therapy: hearing disorder and vertigo.

Laboratory Values
Ribavirin/INTRON A Combination Therapy

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 5**.)
Hemoglobin

Hemoglobin decreases among patients receiving ribavirin therapy began at Week 1, with stabilization by Week 4. In previously untreated patients treated for 48 weeks the mean maximum decrease from baseline was 3.1 g/dL in the US study and 2.9 g/dL in the International study. In relapse patients the mean maximum decrease from baseline was 2.8 g/dL in the US study and 2.6 g/dL in the International study. Hemoglobin values returned to pretreatment levels within 4 to 8 weeks of cessation of therapy in most patients.

Bilirubin and Uric Acid

Increases in both bilirubin and uric acid, associated with hemolysis, were noted in clinical trials. Most were moderate biochemical changes and were reversed within 4 weeks after treatment discontinuation. This observation occurs most frequently in patients with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

TABLE 5. Selected Hematologic Values During Treatment with Ribavirin Capsules plus INTRON A: Previously Untreated and Relapse Adult Patients

	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
	INTRON A plus Ribavirin (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus Ribavirin (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus Ribavirin (N=77)	INTRON A plus Placebo (N=76)
Hemoglobin (g/dL)	24	1	32	1	21	3
9.5-10.9	5	0	4	0	4	0
8-9.4	0	0	0	0.4	0	0
6.5-7.9	0	0	0	0	0	0
<6.5						
Leukocytes ($x10^9$/L)	40	20	38	23	45	26
2-2.9	4	1	9	2	5	3
1.5-1.9	0.9	0	2	0	0	0
1-1.4	0	0	0	0	0	0
<1						
Neutrophils ($x10^9$/L)	30	32	31	44	42	34
1-1.49	14	15	14	11	16	18
0.75-0.99	9	9	14	7	8	4
0.5-0.74	11	8	11	5	5	8
<0.5						
Platelets ($x10^9$/L)	9	11	11	14	6	12
70-99	2	3	2	3	0	5
50-69	0	0.4	0	0.4	0	0
	0.9	0	1	0.9	0	0

30-49 <30						
Total Bilirubin (mg/dL) 1.5 -3 3.1-6 6.1-12 >12	27 0.9 0 0	13 0.4 0 0	32 2 0.4 0	13 0 0 0	21 3 0 0	7 0 0 0

Postmarketing Experiences
The following adverse reactions have been identified during post approval use of ribavirin in combination with INTRON A therapy: hearing disorder, vertigo, aplastic anemia and pure red cell aplasia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

OVERDOSAGE
There is limited experience with overdosage. Acute ingestion of up to 20 grams of ribavirin capsules, INTRON A ingestion of up to 120 million units, and subcutaneous doses of INTRON A up to 10 times the recommended doses have been reported. Primary effects that have been observed are increased incidence and severity of the adverse events related to the therapeutic use of INTRON A and ribavirin. However, hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with administration of single subcutaneous doses of INTRON A that exceed dosing recommendations.

There is no specific antidote for INTRON A or ribavirin overdose, and hemodialysis and peritoneal dialysis are not effective treatment of overdose of either agent.

DOSAGE AND ADMINISTRATION
(see **CLINICAL PHARMACOLOGY, Special Populations**; see **WARNINGS**)

Ribavirin/INTRON A Combination Therapy
The recommended dose of ribavirin capsules depends on the patient's body weight. The recommended dose of ribavirin capsules is provided in **TABLE 6.**

The recommended duration of treatment for patients previously untreated with interferon is 24 to 48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen. (See **Description of Clinical Studies** and **ADVERSE REACTIONS.**) After 24 weeks of treatment virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV RNA below the limit of detection of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in the previously untreated patient population.

In patients who relapse following non-pegylated interferon monotherapy, the recommended duration of treatment is 24 weeks. There are no safety and efficacy data on treatment for longer than 24 weeks in the relapse patient population.
TABLE 6. Recommended Dosing

Body Weight	Ribavirin Capsules
≤ 75 kg	2 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.
> 75 kg	3 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.

Ribavirin capsules may be administered without regard to food, but should be administered in a consistent manner with respect to food intake. (See **CLINICAL PHARMACOLOGY**.)

Under no circumstances should ribavirin capsules be opened, crushed, or broken (see **CONTRAINDICATIONS** and **WARNINGS**).

Dose Modifications (TABLE 7)

If severe adverse reactions or laboratory abnormalities develop during combination ribavirin/INTRON A therapy the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, ribavirin/ INTRON A therapy should be discontinued.

Ribavirin capsules should not be used in patients with creatinine clearance <50 mL/min. Subjects with impaired renal function and/or those over the age of 50 should be carefully monitored with respect to development of anemia. (See **WARNINGS** and **CLINICAL PHARMACOLOGY, Special Populations**.)

Ribavirin capsules should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped. (See **WARNINGS**.)

For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by ≥2 g/dL during any 4-week period. In addition, for these cardiac history patients, if the hemoglobin remains <12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination ribavirin/INTRON A therapy.

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her ribavirin dose reduced to 600 mg daily (1 x 200 mg capsule AM, 2 x 200 mg capsules PM) for adults and 7.5 mg/kg per day (divided dose AM and PM) for pediatric patients.A patient whose hemoglobin level falls below 8.5 g/dL should be permanently discontinued from ribavirin therapy. (See **WARNINGS**.)

TABLE 7. Guidelines for Dose Modifications and Discontinuation for Anemia

	Dose Reduction* Ribavirin - 600 mg daily adults	Permanent Discontinuation of Ribavirin Treatment
Hemoglobin		
No Cardiac History	**<10 g/dL**	**<8.5 g/dL**
Cardiac History Patients	**≥2 g/dL decrease during any 4-week period during treatment**	**<12 g/dL after 4 weeks of dose reduction**

HOW SUPPLIED

Ribavirin Capsules, 200 mg are white/white, size '1' hard gelatin capsule filled with white to off-white granular powder and imprinted with 'E' on white cap and '81' on white body with black ink.

Bottles of 42	NDC 65862-290-42
Bottles of 56	NDC 65862-290-56
Bottles of 70	NDC 65862-290-70
Bottles of 84	NDC 65862-290-84
Bottles of 180	NDC 65862-290-18
Bottles of 500	NDC 65862-290-05

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Mylanta is a registered trademark of Johnson & Johnson-Merck Consumer Pharmaceuticals Co.

Intron A is a registered trademark of Schering Corporation.

Manufactured for:
Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

Manufactured by:
Aurobindo Pharma Limited
Hyderabad-500 072, India
Revised: 10/2009

MEDICATION GUIDE
Ribavirin Capsules 200 mg
Rx only

Read this medication guide carefully before you begin taking ribavirin capsules, and each time you refill your prescription in case new information has been included. This summary does not tell you everything about ribavirin capsules. Your health care provider is the best source of information about this medicine. After reading this medication guide, talk with your health care provider if you have any questions about ribavirin.

What is the most important information I should know about therapy with ribavirin capsules?

- **Ribavirin capsules may cause birth defects or death of an unborn child. Therefore, if you are pregnant or your sexual partner is pregnant, do not take ribavirin.** If you could become pregnant, you must not become pregnant during therapy and for 6 months after you have stopped therapy. During this time you must use 2 forms of birth control, and you must have pregnancy tests that show that you are not pregnant.

Female sexual partners of male patients being treated with ribavirin must not become pregnant during treatment and for 6 months after treatment has stopped. Therefore, you must use 2 forms of birth control during this time.
If you or a female sexual partner becomes pregnant, you should tell your health care provider. There is a Ribavirin Pregnancy Registry that collects information about pregnancy outcomes in female patients and female partners of male patients exposed to ribavirin. You or your health care provider are encouraged to contact the Registry at 1-800-593-2214.

Be assured that any information you tell the Registry will be kept confidential. (See **"What should I avoid while taking ribavirin capsules?"**)

- **Ribavirin capsules can cause a dangerous drop in your red blood cell count.** Ribavirin capsules can cause anemia, which is a decrease in the number of red blood cells. This can be dangerous, especially if you have heart or breathing problems. Tell your health care provider before taking ribavirin if you have ever had any of these problems. Your health care provider should check your red blood cell count before you start therapy and often during the first 4 weeks of therapy. Your red blood cell count may be checked more often if you have any heart or breathing problems.

- **Do not take ribavirin capsules alone to treat hepatitis C infection.** Ribavirin capsules should be used in combination with interferon alfa-2b (INTRON A) for treating chronic hepatitis C infection in adults. In children, safety and effectiveness of ribavirin capsules has only been shown when used in combination with interferon alfa-2b (INTRON A). Your health care provider or pharmacist should give you a copy of the INTRON A Medication Guide. It has additional important information about combination therapy not covered in this guide.

What is ribavirin?
Ribavirin is an antiviral drug. It is used in combination with interferon alfa-2b to treat some patients with chronic hepatitis C infection. It is not known how ribavirin and interferon alfa-2b work together to fight hepatitis C infection (see the INTRON A Medication Guide).

It is not known if treatment with ribavirin and interferon alfa-2b will cure hepatitis C virus infections or prevent cirrhosis, liver failure, or liver cancer that can be caused by hepatitis C virus infections. It is not known if treatment with ribavirin and interferon alfa-2b will prevent an infected person from infecting another person with the hepatitis C virus.

Who should not take ribavirin capsules?
Do not use these medicines if:

- You are a female and you are pregnant or plan to become pregnant at any time during your treatment with ribavirin or during the 6 months after your treatment has ended.

- You are a male patient with a female sexual partner who is pregnant or plans to become pregnant at any time while you are being treated with ribavirin or during the 6 months after your treatment has ended. (See **"What is the most important information I should know about therapy with ribavirin capsules?"** and **"What should I avoid while taking ribavirin capsules?"**)

- You are breast-feeding. Ribavirin may pass through your milk and harm your baby. Talk with your provider about whether you should stop breast-feeding.

- You are allergic to any of the ingredients in ribavirin capsules. See the ingredients listed at the end of this Medication Guide.

Tell your health care provider before starting treatment with ribavirin capsules in combination with interferon alfa-2b if you have any of the following medical conditions:

- **mental health problems, such as depression or anxiety.** Ribavirin/interferon alfa-2b therapy may make them worse. Tell your healthcare provider if you are being treated or had treatment in the past for any mental problems, including depression, suicidal behavior, or a feeling of loss of contact with reality, such as hearing voices or seeing things that are not there (psychosis). Tell your health care provider if you take any medicines for these problems.
- **high blood pressure, heart problems, or have had a heart attack.** Ribavirin capsules may worsen heart problems. Patients who have had certain heart problems should not take ribavirin capsules.
- **blood disorders,** including anemia (low red blood cell count), thalassemia (Mediterranean anemia) and sickle-cell anemia. Ribavirin capsules can reduce the number of red blood cells you have. This may make you feel dizzy or weak and could worsen any heart problems you might have.
- **kidney problems.** If your kidneys do not work properly, you may experience worse side effects from ribavirin therapy and require a lower dose.
- **liver problems** (other than hepatitis C infection).
- **organ transplant,** and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system).
- **thyroid disease.** Ribavirin/interferon alfa-2b therapy may make your thyroid disease worse or harder to treat. Ribavirin/interferon alfa-2b therapy may be stopped if you develop thyroid problems that cannot be controlled by medicine.
- **lung problems.** Ribavirin/interferon alfa-2b therapy can cause breathing problems or worsen breathing problems you already have.
- **alcoholism or drug abuse or addiction**
- **cancer**
- **infection with hepatitis B virus and/or human immunodeficiency virus** (the virus that causes AIDS).
- **diabetes.** Ribavirin/interferon alfa-2b therapy may make your diabetes worse or harder to treat.
- **past interferon treatment for hepatitis C virus infection that did not work for you.**

For more information see the INTRON A Medication Guide.

How should I take ribavirin capsules?
Your health care provider has determined the correct dose of ribavirin capsules based on your weight. Your health care provider may lower your dose of ribavirin if you have side effects.

- It is important to follow your dosing schedule and your health care provider’s instructions on how to take your medicines.
- Under no circumstances should ribavirin capsules be opened, crushed, or broken.
- You should take ribavirin with food. Taking ribavirin with food helps your body take up more of the medicine. Taking ribavirin at the same time of day every day will help keep the amount of medicine in your body at steady level. This can help your health care provider decide how your treatment is working and how to change the number of ribavirin capsules you take if you have side effects.
- Take the medicine for as long as prescribed and do not take more than the recommended dose.
- If you miss a dose of ribavirin capsules, take the missed dose as soon as possible during the same day. If an entire day has gone by, check with your health care provider about what to do. Do not double the next dose.
- Tell your health care provider if you are taking or planning to take other prescription or non-prescription medicines, including vitamin and mineral supplements, and herbal medicines.
- Tell your provider before taking ribavirin capsules if you have ever had any heart or breathing problems. Your provider should check your red blood cell count before starting therapy and often during the first 4 weeks of therapy. Your red blood cell count may be checked more frequently if you have had heart or breathing problems.
- Females taking ribavirin capsules or female sexual partners of male patients taking ribavirin capsules must have a pregnancy test before treatment begins, every month during treatment, and for 6 months after treatment ends to make sure there is no pregnancy.

What should I avoid while taking ribavirin capsules?
Avoid the following during ribavirin capsule treatment:

- **Pregnancy:** If you or your sexual partner gets pregnant during treatment with ribavirin capsules or in the 6 months after treatment ends, tell your health care provider right away. (See **"What is the most important information I should know about therapy with ribavirin capsules?"**)

Talk with your health care provider about how to avoid pregnancy. If you or your sexual partner get pregnant while on ribavirin or during the 6 months after your treatment ends, you must report the pregnancy to your health care provider right away. Your health care provider should call 1-800-593-2214. Your health care provider will be asked to give follow-up information about the pregnancy. Any information about your pregnancy that is reported about you will be confidential.

- **Breast-feeding.** The medicine may pass through your milk and harm the baby.
- **Drinking alcohol,** including beer, wine, and liquor. This may make your liver disease worse.
- **Taking other medicines.** Take only medicines prescribed or approved by your health care provider. These include prescription and nonprescription medicines and herbal supplements.

What are the most common side effects of ribavirin capsules?
The most serious possible side effects of ribavirin capsules are:

- **Harm to unborn children.** Ribavirin capsules may cause birth defects or death of an unborn child. (For more details, see **"What is the most important information I should know about therapy with ribavirin capsules?"**)
- **Anemia.** Anemia is a reduction in the number of red blood cells you have which can be dangerous, especially if you have heart or breathing problems. Tell your health care provider right away if you feel tired, have chest pain or shortness of breath. These may be signs of low red blood cell counts.

Tell your provider right away if you have any of the following symptoms. They may be signs of a serious side effect:

- **trouble breathing**
- **hives or swelling**
- **chest pain**
- **severe stomach or low back pain**
- **bloody diarrhea or bloody stools (bowel movements). These may appear black and tarry.**
- **bruising**
- **other bleeding**

The most common side effects of ribavirin capsules are:

- **feeling tired**
- **nausea and appetite loss**
- **rash and itching**
- **cough**

This summary does not include all possible side effects of ribavirin therapy. Talk to your health care provider if you do not feel well while taking ribavirin. Your health care provider can give you more information about managing your side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

What should I know about hepatitis C infection?
Hepatitis C infection is a disease caused by a virus that infects the liver. This liver infection becomes a continuing (chronic) condition in most patients. Patients with chronic hepatitis C infection may develop cirrhosis, liver cancer, and liver failure. The virus is spread

from one person to another by contact with the infected person's blood. You should talk to your health care provider about ways to prevent you from infecting others.

How do I store my ribavirin capsules?
Store ribavirin capsules at room temperature 77°F (25°C).

General advice about prescription medicines
Do not use ribavirin capsules for conditions for which they were not prescribed. If you have any concern about ribavirin capsules, ask your health care provider. Your health care provider or pharmacist can give you information about ribavirin capsules that was written for health care professionals. Do not give this medicine to other people, even if they have the same condition you have.

For more information call 1-866-850-2876.
Ingredients:

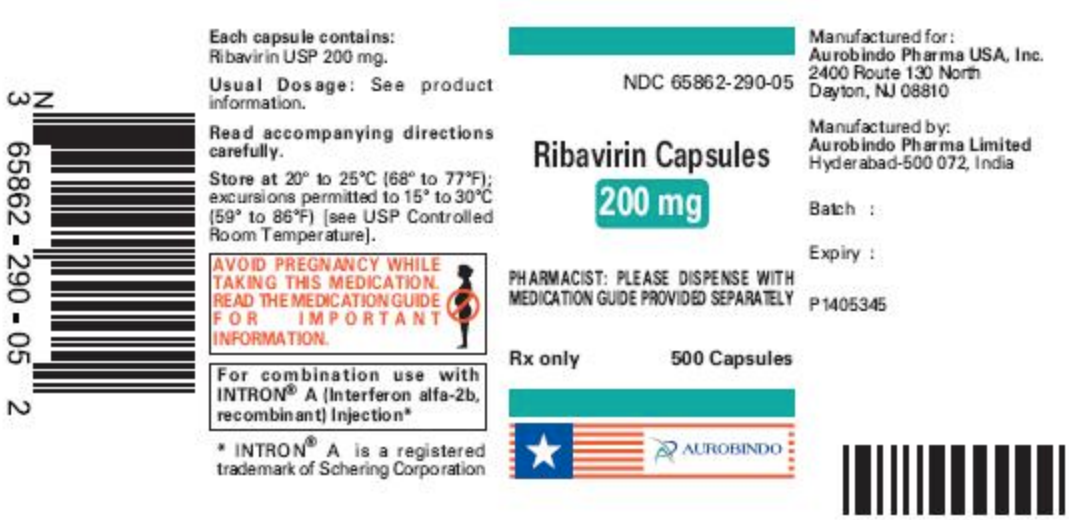
Ribavirin capsules contain ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, povidone-K 30, and magnesium stearate. The capsule shell consists of titanium dioxide, sodium lauryl sulfate, and gelatin. The capsule is printed with edible ink containing black iron oxide.
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Intron A is a registered trademark of Schering Corporation.
Manufactured for:
Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

Manufactured by:
Aurobindo Pharma Limited
Hyderabad-500 072, India

Revised: 10/2009

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 200 MG (500 CAPSULE BOTTLE)
NDC 65862-290-05
Ribavirin Capsules
200 mg
PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY
Rx only 500 Capsules
AUROBINDO



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